

## WE CLAIM:

1. An isolated mutant prohormone convertase 1 (PC1) polypeptide comprising a missense mutation at residue Asn<sup>222</sup> in the catalytic domain.
2. The mutant prohormone convertase 1 of claim 1, wherein the missense mutation is substitution of Asn<sup>222</sup> with an acidic amino acid residue.
3. The mutant prohormone convertase 1 of claim 2, wherein the acidic amino acid residue is aspartic acid.
4. The mutant prohormone convertase 1 of claim 1, wherein the prohormone convertase 1 is from a mammalian species.
5. The mutant prohormone convertase 1 of claim 4, wherein the prohormone convertase 1 is from human.
6. The mutant prohormone convertase 1 of claim 5, wherein the human prohormone convertase has an amino acid sequence of accession number NP\_000430, P29120, or KXHUC1.
7. The mutant prohormone convertase 1 of claim 4, wherein the prohormone convertase 1 is from mouse.
8. The mutant prohormone convertase 1 of claim 7, wherein the mouse prohormone convertase has an amino acid sequence of accession number NP\_038656 or KXMSC1.
9. An isolated polynucleotide encoding a mutant prohormone convertase 1 (PC1) polypeptide, wherein the mutant prohormone convertase polypeptide comprises a missense mutation at residue Asn<sup>222</sup> in the catalytic domain.
10. The polynucleotide of claim 9, wherein the missense mutation is substitution of Asn<sup>222</sup> with an acidic amino acid residue.
11. The polynucleotide of claim 10, wherein the acidic amino acid residue is aspartic acid.

12. The polynucleotide of claim 9, wherein the prohormone convertase 1 is from a mammalian species.
13. The polynucleotide of claim 12, wherein the prohormone convertase 1 is from human.
14. The polynucleotide of claim 13, wherein the human prohormone convertase 1 is encoded by a polynucleotide sequence having accession number NM\_000439 or X64810.
15. The polynucleotide of claim 12, wherein the prohormone convertase 1 is from mouse.
16. The polynucleotide of claim 15, wherein the mouse prohormone convertase 1 is encoded by a polynucleotide sequence having accession number NM\_013628, M69196, or M58589.
17. A non-human animal which comprises a mutant prohormone convertase 1 (PC1) gene encoding a mutant prohormone convertase 1 polypeptide, wherein the mutant prohormone convertase 1 polypeptide comprises a missense mutation at residue Asn<sup>222</sup> in the catalytic domain.
18. The non-human animal of claim 17, wherein the missense mutation is substitution of Asn<sup>222</sup> with an acidic amino acid residue.
19. The non-human animal of claim 18, wherein the acidic amino acid residue is aspartic acid.
20. The non-human animal of claim 17, wherein the PC1 gene is from a mammalian species.
21. The non-human animal of claim 20 which is a mouse, wherein the PC1 gene is mouse PC1 gene.
22. The non-human animal of claim 20 which is a rat, wherein the PC1 gene is rat PC1 gene.

23. A non-human animal comprising, in its genome, a DNA sequence encoding a mutant PC1 polypeptide that is defective in its autocatalytic activity relative to wildtype form of the PC1 polypeptide.
24. The non-human animal of claim 23, wherein said mutant PC1 polypeptide comprises a missense mutation at residue N222.
25. The non-human animal of claim 24, wherein the missense mutation is substitution of N222 with an acidic residue.
26. The non-human animal of claim 25, wherein the acidic residue is Asp.
27. The non-human animal of claim 23, wherein the mutant PC1 polypeptide is mouse PC1 polypeptide.
28. The non-human animal of claim 23, wherein the mutant PC1 polypeptide is encoded by a transgene heterologous to the animal.